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(54) Title: **CHK1 KINASE INHIBITORS**

(57) Abstract: Novel compounds useful in the inhibition of damage response kinases are provided.



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## **CHK1 KINASE INHIBITORS**

### **FIELD OF THE INVENTION**

The present invention relates to damage response kinase inhibitors, especially checkpoint kinase ("chk1 kinase") inhibitors, pharmaceutical compositions comprising these compounds and methods of using these compounds to treat various forms of cancer and hyperproliferative disorders.

### **BACKGROUND OF THE INVENTION**

The cellular response to DNA damage involves cell cycle delays, increased repair, and apoptosis (Zhou and Elledge *Nature* 2000 408: 433-439). Although many effective cancer therapies work by causing DNA damage induced apoptosis, resistance to these agents remains a significant limitation in the treatment of cancer. One important mechanism of drug resistance is attributed to cell cycle delays (also called checkpoints) and repair activation, which provides both the opportunity and capacity for cells to repair DNA damage. It is likely that approaches abrogating these survival DNA damage responses would have significant clinical utility.

Among different DNA damage response kinases, Chk1 was linked to survival responses including checkpoints. Mice lacking CHK1 die in early embryogenesis (Liu et al. *Gene & Dev.* 2000 14: 1448-1459; Takai et al. *Gene & Dev.* 2000 14: 1439-1447). ES cells expressing a conditional *CHK1* gene die of p53-independent apoptosis after loss of CHK1. Prior to their death, these cells become incapable of preventing mitotic entry in response to IR (Liu et al. *Gene & Dev.* 2000 14: 1448-1459), demonstrating that Chk1 is required for the G2 DNA damage checkpoint in mammals as previously observed in other organisms.

Chk1 prevents mitotic entry as follows. Arrest in G2 is regulated by the maintenance of inhibitory phosphorylation of Cdc2 (Nurse *Cell* 1997 91: 865-867). Cdc2 dephosphorylation and activation is catalyzed by the dual specificity phosphatase Cdc25 (Morgan *Nature* 1995 374: 131-134). Recent evidence indicates that part of the G2/M DNA checkpoint mechanism involves inactivation and translocation of Cdc25C into the cytoplasm. This is at least partially mediated by

phosphorylation on Ser-216 in Cdc25C and its consequent binding with 14-3-3 proteins (Peng et al. *Science* 1997 277: 1501-1505; Dalal et al. *Mol. Cell Bio.* 1999 19: 4465-4479; Yang et al. *EMBO J.* 1999 18: 2174-2183). Chk1 (Sanchez et al. *Science* 1997 277: 1497-1501) has been shown to phosphorylate Cdc25C at Ser-216 *in vitro*. This modification is thought to maintain Cdc25C phosphorylation in cells arrested at G2/M in response to DNA damage. Recently, staurosporine-like kinase inhibitors, UCN-01 and SB-218078, have been shown to be potent Chk1 inhibitors (Jackson et al. *Cancer Res.* 2000 60: 566-572; Graves et al. *J. Biol. Chem.* 2000 275: 5600-5605). *In vivo*, they can abrogate the G2/M checkpoint induced by DNA damaging agents and enhance the cytotoxicities of the DNA damaging agents. Thus it is likely that a specific Chk1 inhibitor could be used clinically in combination treatment with conventional therapies. Since Chk1 is an essential kinase for regular cell cycle (Liu et al., *Gene & Dev.* 2000 14: 1448-1459), it is possible that Chk1 inhibitors could also be used alone in cancer therapy.

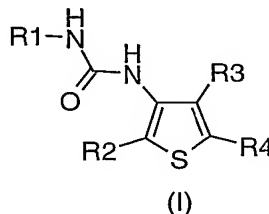
Based on the foregoing, there is a need to identify a potent chk1 kinase inhibitors for the treatment of the various aforementioned indications.

### **SUMMARY OF THE INVENTION**

The present invention involves 3-ureidothiophene compounds represented by Formula (I) hereinbelow, pharmaceutical compositions comprising such compounds and methods of inhibiting chk1 kinase as well as specific assays to detect inhibition of chk1 kinase activity.

### **DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides compounds of Formula (I), hereinbelow:



wherein:

R1 is selected from the group consisting of H, C<sub>1-2</sub> alkyl, XH, XCH<sub>3</sub>, C<sub>1-2</sub> alkyl-XH, C<sub>1-2</sub> alkyl-XCH<sub>3</sub>, C(O)NH<sub>2</sub>, C(O)NHCH<sub>3</sub>, and C(O)-C<sub>1-2</sub> alkyl, with the preferred substitution being H or CH<sub>3</sub>;

X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of C(O)R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, C(O)NHR<sup>5</sup>, C(O)NHC(=NH)R<sup>5</sup>, C(O)NHC(=NH)NR<sup>5</sup>R<sup>6</sup>, C(O)NHC(O)R<sup>5</sup>, C(O)NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>5</sup>, S(O)R<sup>5</sup>, SO<sub>3</sub>R<sup>5</sup>, and PO<sub>3</sub>R<sup>5</sup>R<sup>6</sup>;

R<sup>5</sup> and R<sup>6</sup> are, independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, and C<sub>0-6</sub> alkylheteroaryl, or R<sup>5</sup> and R<sup>6</sup>, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl, wherein any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen, with the preferred substitution being H;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position;

A is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, C<sub>0-6</sub> alkylheteroaryl, C(=NH)R<sup>7</sup>, COR<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>, C(S)R<sup>7</sup>, cyano, trifluoromethyl, NR<sup>7</sup>R<sup>8</sup>, N(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>Y, NR<sup>7</sup>COR<sup>7</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CON(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>Y, NR<sup>7</sup>CO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>C(O)SR<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, nitro, OR<sup>7</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>7</sup>, S(O)R<sup>7</sup>, S(O)<sub>2</sub>R<sup>7</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>3</sub>R<sup>7</sup>, PO<sub>3</sub>R<sup>7</sup>R<sup>8</sup>, and halo, wherein C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, C<sub>0-6</sub> alkylheteroaryl, (CH<sub>2</sub>)<sub>0-6</sub>heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion including, but not limited to, bisulfate, chloride, fumarate, iodide, maleate, methanesulfonate, trifluoromethanesulfonate, nitrate, or sulfate;

D is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, C<sub>0-6</sub> alkylheteroaryl, C(=NH)R<sup>7</sup>, COR<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>, C(S)R<sup>7</sup>, cyano, trifluoromethyl, NR<sup>7</sup>R<sup>8</sup>, N(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>Y, NR<sup>7</sup>COR<sup>7</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CON(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>Y, NR<sup>7</sup>CO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>C(O)SR<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, nitro, OR<sup>7</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>7</sup>, S(O)R<sup>7</sup>, S(O)<sub>2</sub>R<sup>7</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>3</sub>R<sup>7</sup>, PO<sub>3</sub>R<sup>7</sup>R<sup>8</sup>, and halo, wherein C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, C<sub>0-6</sub> alkylheteroaryl, (CH<sub>2</sub>)<sub>0-6</sub>heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are, independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, and C<sub>0-6</sub> alkylheteroaryl, or R<sup>7</sup> and R<sup>8</sup>, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl, wherein any of the foregoing may be optionally substituted by one or more of group E and on any position;

E is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, C<sub>0-6</sub> alkylheteroaryl, C(=NH)R<sup>10</sup>, COR<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, CON(O)R<sup>10</sup>R<sup>11</sup>, CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, CO<sub>2</sub>R<sup>10</sup>, C(O)SR<sup>10</sup>, C(S)R<sup>10</sup>, cyano, trifluoromethyl, NR<sup>10</sup>R<sup>11</sup>, N(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>COR<sup>10</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CON(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>CO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>C(O)SR<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, nitro, OR<sup>10</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>10</sup>, S(O)R<sup>10</sup>, S(O)<sub>2</sub>R<sup>10</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, SO<sub>3</sub>R<sup>10</sup>, PO<sub>3</sub>R<sup>10</sup>R<sup>11</sup>, and halo, wherein C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, C<sub>0-6</sub> alkylheteroaryl

may be optionally substituted by one or more of  $C(=NH)R^{10}$ ,  $COR^{10}$ ,  $CONR^{10}R^{11}$ ,  $CON(O)R^{10}R^{11}$ ,  $CONR^{10}R^{11}R^{12}Y$ ,  $CO_2R^{10}$ ,  $C(O)SR^{10}$ ,  $C(S)R^{10}$ , cyano, trifluoromethyl,  $NR^{10}R^{11}$ ,  $N(O)R^{10}R^{11}$ ,  $NR^{10}R^{11}R^{12}Y$ ,  $NR^{10}COR^{10}$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}CON(O)R^{10}R^{11}$ ,  $NR^{10}CONR^{10}R^{11}R^{12}Y$ ,  $NR^{10}CO_2R^{10}$ ,  $NR^{10}C(O)SR^{10}$ ,  $NR^{10}SO_2R^{10}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ , nitro,  $OR^{10}$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^{10}$ ,  $S(O)R^{10}$ ,  $S(O)_2R^{10}$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^{10}R^{11}$ ,  $SO_3R^{10}$ ,  $PO_3R^{10}R^{11}$ , or halo, and on any position;  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$  are, independently, selected from the group consisting of hydrogen,  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl, and  $C_{0-6}$  alkylheteroaryl; or  $R^{10}$  and  $R^{11}$ , taken together with the nitrogen to which they are attached, forms a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen,  $C_{1-6}$  alkyl or  $(CH_2)_{0-3}$ aryl.

This invention also covers pharmaceutically acceptable inorganic or organic salts, esters, and other prodrugs of formula (I).

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined together by single carbon-carbon bonds. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Preferably, the group is saturated linear or cyclic.

The term "alkanoyl" is used herein at all occurrences to mean a  $C(O)$ alkyl group, wherein the alkyl portion is as defined below, including, but not limited to, acetyl, pivaloyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean a straight or branched chain radical, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

The term "alkylaryl" is used herein at all occurrences to mean an aryl group as defined below attached to an alkyl group as defined above, including, but not limited to, benzyl and phenethyl, and the like.

The term "alkylheterocyclyl" is used herein at all occurrences to mean a heterocyclic group as defined below attached to an alkyl group as defined above, including, but not limited to, (tetrahydro-3-furanyl)methyl and 3-(4-morpholinyl)propyl, and the like.

The term "alkylheteroaryl" is used herein at all occurrences to mean a heteroaryl group as defined below attached to an alkyl group as defined above, including, but not limited to, 3-(furanyl)methyl and (2-pyridinyl)propyl, and the like.

The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical, wherein there is at least one triple bond between two of the carbon atoms in the chain, including, but not limited to, acetylene, 1-propylene, 2-propylene, and the like.

The term "aralkyl" is used herein at all occurrences to mean an aryl moiety as defined below, which is connected to an alkyl moiety as defined above, including, but not limited to, benzyl or phenethyl, and the like.

The term "aryl" is used herein at all occurrences to mean 6-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to phenyl, naphthalenyl, biphenyl, phenanthryl, anthracenyl, and the like.

The term "aryloxy" is used herein at all occurrences to mean an aryl group as defined above linked via an oxy group, including, but not limited to, phenoxy, and the like.

The terms "cycloalkyl" is used herein at all occurrences to mean cyclic radicals, which may be mono- or bicyclo- fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heteroaryl" is used herein at all occurrences to mean a 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, which ring or ring systems contain 1 to 4 heteroatoms selected from nitrogen, which may be optionally substituted with hydrogen or C<sub>1</sub>-alkyl, oxygen, and sulfur, including, but not limited to, indolyl, benzofuranyl, thianaphthenyl, quinolyl, isoquinolyl, pyrrolyl, furanyl, thienyl, pyridyl, and the like.

The term "heteroaryloxy" is used herein at all occurrences to mean an heteroaryl group as defined above linked via an oxy group, including, but not limited to, 2-pyridinyloxy, and the like.

The term "heterocyclic" is used herein at all occurrences to mean a saturated or wholly or partially unsaturated 5-10-membered ring system (unless the cyclic ring system is otherwise limited) in which one or more rings contain one or more heteroatoms selected from nitrogen, which may be optionally substituted with hydrogen or C<sub>1</sub>-alkyl, oxygen, and sulfur, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, 1,2,3,6-tetrahydropyridine, hexahydroazepine, and the like.

Preferred compounds useful in the present invention include:

4-Ureido-[2,3']bithiophenyl-5-carboxylic acid amide  
5-(4-Methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid amide  
5-(4-Fluoro-phenyl)-3-ureido-thiophene-2-carboxylic acid amide  
5-Phenyl-3-ureido-thiophene-2-carboxylic acid methyl ester  
1-(2-Acetyl-5-phenyl-thiophen-3-yl)-3-methyl-urea  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid amide  
5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid amide  
3-(3-Methyl-ureido)-5-phenyl-thiophene-2-carboxylic acid methyl ester  
5-(4-Fluoro-phenyl)-3-ureido-thiophene-2-carboxylic acid methyl ester  
(2-Acetyl-5-phenyl-thiophen-3-yl)-urea  
5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
5-(4-Methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid methylamide  
5-(3,4-Dimethoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide

4-(3-Ethyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide  
4-biuret-[2,3']bithiophenyl-5-carboxylic acid methylamide  
5-(4-Amino-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
4-(3-Hydroxymethyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid phenylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzo[1,3]dioxol-5-ylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (4-methoxy-phenyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-hydroxy-phenyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid ethylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid propylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid isopropylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid isobutyl-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid pyrrolidin-3-ylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-methoxy-ethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-amino-ethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (3-dimethylamino-propyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (3-amino-2-hydroxy-propyl)-amid  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (pyridin-4-ylmethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (furan-2-ylmethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (1*H*-imidazol-2-ylmethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

More preferred compounds useful in the present invention include:

4-Ureido-[2,3']bithiophenyl-5-carboxylic acid amide  
5-(4-Methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid amide  
5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid amide  
5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
5-(3,4-Dimethoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid phenylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzo[1,3]dioxol-5-ylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-amino-ethyl)-amide

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

Geometric isomers and tautomers of the present compounds are also within the scope of the present invention.

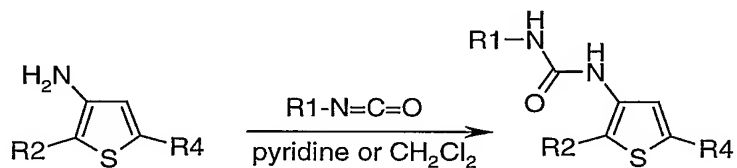
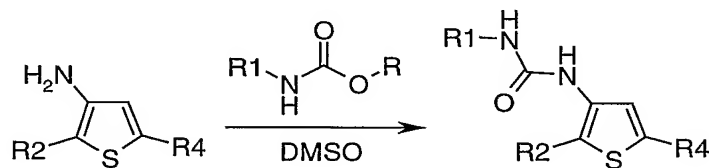
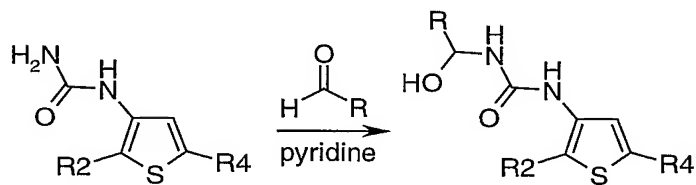
The present compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present.

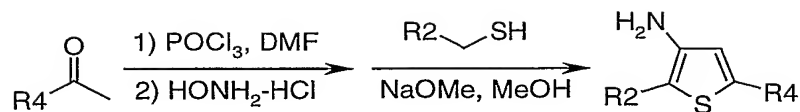
Thiophenes of formula (I) can be prepared readily from various commercially-available 3-aminothiophenes. Treatment of the 3-aminothiophene with an isocyanate, for example methyl isocyanate or chlorosulfonyl isocyanate, under standard conditions, for example in pyridine or dichloromethane from 23-50 °C, affords the corresponding 3-ureidothiophene (Scheme I). Treatment of the 3-

aminothiophene with a carbamic ester (for example, ethyl allophanate) in a solvent such as dimethylsulfoxide at elevated temperatures such as 80-100 °C can also provide 3-ureidothiophene derivatives (Scheme II). More diverse urea compounds can be prepared using standard alkylation methods, such as the use of an aldehyde (for example, formaldehyde) in pyridine, of a 3-ureidothiophene as indicated in Scheme III.

**Scheme I****Scheme II****Scheme III**

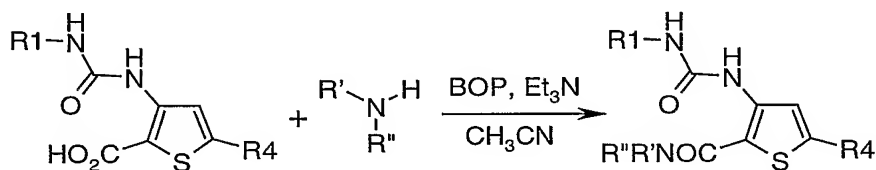
Alternatively, the 3-aminothiophenes can be prepared following published procedures (for example, WO200158890A1) starting from commercially-available aryl methyl ketones and mercapto derivatives (for example, mercapto acetic acid methyl ester and mercapto methyl acetamide; Scheme IV). The corresponding 3-ureidothiophenes can then be prepared as stated above.

**Scheme IV**



Further elaboration of the R2 position can occur starting from a suitable 3-ureidothiophene precursor, such as a 3-(3-methyl-ureido)-5-aryl-thiophene-2-carboxylic acid. Utilizing known amine coupling methods with the carboxylic acid, for example the use of BOP and an amine in the presence of a base, for example triethylamine, in a solvent, such as acetonitrile, will lead to variously-substituted 2-amido-3-ureidothiophenes (Scheme V).

Scheme V



The following experimentals are intended to illustrate the embodiments of the present invention only, but not be limiting in any way.

### Example 1

#### Preparation of 5-phenyl-3-ureido-thiophene-2-carboxylic acid methyl ester

To a room temperature solution of 3-amino-5-phenyl-2-thiophene carboxylic acid methyl ester (0.20 mmol) in dichloromethane (1.0 mL) was added chlorosulfonyl isocyanate (0.22 mmol). The reaction mixture was stirred for 4 h, quenched with the addition of water (0.5 mL), and then stirred overnight. After concentrating in vacuo, the reaction mixture was dissolved in DMSO and purified by Gilson reverse phase HPLC to afford the title product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.56 (br s, 1H), 8.26 (s, 1H), 7.68 (d, 2H,  $J = 8.1$  Hz), 7.40 (m, 3H), 4.81 (br s, 2H), 3.89 (s, 3H). ESIMS  $[\text{M}+\text{H}]^+$ : 276.2.

### **Example 2**

#### **Preparation of 1-(2-acetyl-5-phenyl-thiophen-3-yl)-3-methyl-urea**

To a room temperature solution of 2-acetyl-3-amino-5-phenyl-thiophene (0.23 mmol) in pyridine (1.0 mL) was added methyl isocyanate (0.42 mmol). The reaction mixture was stirred 40 h at 50 °C, cooled, and then diluted with methanol and concentrated in vacuo. The reaction mixture was dissolved in DMSO and purified by Gilson reverse phase HPLC to provide the title compound. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.20 (br s, 1H), 8.36 (s, 1H), 7.72 (d, 2H, *J* = 6.8 Hz), 7.68 (br s, 1H), 7.49 (m, 3H), 2.66 (d, 3H, *J* = 4.4 Hz), 2.44 (s, 3H). ESIMS [M+H]<sup>+</sup>: 275.0.

### **Example 3**

#### **Preparation of (2-acetyl-5-phenyl-thiophen-3-yl)-urea**

Following the procedure described in Example 1 with 2-acetyl-3-amino-5-phenyl-thiophene provided the title compound. ESIMS [M+H]<sup>+</sup>: 261.2.

### **Example 4**

#### **Preparation of 4-(3-methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid amide**

To a room temperature solution of 4-amino-[2,3']bithiophenyl-5-carboxamide (0.22 mmol) in pyridine (1.0 mL) was added methyl isocyanate (0.42 mmol). The reaction mixture was stirred overnight and then diluted with methanol and concentrated in vacuo. The reaction mixture was dissolved in DMSO and purified by Gilson reverse phase HPLC to provide the title compound. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.16 (br s, 1H), 8.11 (s, 1H), 7.82 (dd, 1H, *J* = 2.9, 1.3 Hz), 7.69 (dd, 1H, *J* = 5.0, 2.9 Hz), 7.39 (br s, 3H), 7.36 (dd, 1H, *J* = 5.0, 1.4 Hz), 2.63 (3, 3H, *J* = 4.5 Hz). ESIMS [M+H]<sup>+</sup>: 283.2.

### **Example 5**

Preparation of 5-(4-methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid amide

Following the procedure described in Example 4 with 3-amino-5-(4-methoxy-phenyl)-2-thiophene carboxamide provided the title compound.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.17 (br s, 1H), 8.13 (s, 1H), 7.56 (d, 2H,  $J = 8.7$  Hz), 7.38 (br s, 3H), 7.03 (d, 2H,  $J = 8.8$  Hz), 3.80 (s, 3H), 2.63 (d, 3H,  $J = 4.4$  Hz). ESIMS  $[\text{M}+\text{H}]^+$ : 306.0.

**Example 6**

Preparation of 3-(3-methyl-ureido)-5-phenyl-thiophene-2-carboxylic acid methyl ester

Following the procedure described in Example 2 with 3-amino-5-phenyl-2-thiophene carboxylic acid methyl ester provided the title compound. ESIMS  $[\text{M}+\text{H}]^+$ : 291.0.

**Example 7**

Preparation of 4-ureido-[2,3'-bithiophenyl-5-carboxylic acid amide

Following the procedure described in Example 1 with 4-amino-[2,3'-bithiophenyl-5-carboxamide provided the title compound.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.08 (s, 1H), 7.70 (dd, 1H,  $J = 2.9, 1.3$  Hz), 7.53 (dd, 1H,  $J = 5.1, 2.9$  Hz), 7.39 (dd, 1H,  $J = 5.1, 1.3$  Hz).

### **Example 8**

#### **Preparation of 5-(4-methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid amide**

Following the procedure described in Example 1 with 3-amino-5-(4-methoxy-phenyl)-2-thiophene carboxamide provided the title compound. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.07 (s, 1H), 8.12 (s, 1H), 7.55 (d, 2H, *J* = 8.8 Hz), 7.38 (br s, 2H), 7.03 (d, 2H, *J* = 8.8 Hz), 6.61 (br s, 2H), 3.80 (s, 3H).

### **Example 9**

#### **Preparation of 5-(4-fluoro-phenyl)-3-ureido-thiophene-2-carboxylic acid amide**

Following the procedure described in Example 1 with 3-amino-5-(4-fluoro-phenyl)-2-thiophene carboxamide provided the title compound. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.06 (s, 1H), 8.21 (s, 1H), 7.67 (m, 2H), 7.46 (br s, 2H), 7.31 (m, 2H), 6.67 (br s, 2H).

### **Example 10**

#### **Preparation of 5-(4-fluoro-phenyl)-3-ureido-thiophene-2-carboxylic acid methyl ester**

Following the procedure described in Example 1 with 3-amino-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid methyl ester provided the title compound. ESIMS [M+H]<sup>+</sup>: 295.2.

### **Example 11**

#### **Preparation of 4-biuret-[2,3]bithiophenyl-5-carboxylic acid methylamide**

##### **a) 4-Amino-[2,3]bithiophenyl-5-carboxylic acid methylamide**

Phosphorous oxychloride (17 mmol) was added to an ice-cooled solution of *N,N*-dimethylformamide (3.0 mL). After 35 min, 1-thiophen-3-yl-ethanone (7.9 mmol) was added portionwise and the resulting mixture was heated briefly at 50 °C

until the solution was homogeneous. Hydroxylamine hydrochloride (36 mmol) was added slowly to the reaction mixture at room temperature. The reaction mixture was stirred for 30 min, quenched with the addition of water, and stirred for an additional 30 min. The reaction mixture was poured into water and the organics were extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, were filtered, and were concentrated by rotary evaporation. The crude oil was diluted with methanol (5.0 mL). 2-Mercapto-*N*-methyl-acetamide (12 mmol) and sodium methoxide (12 mmol of a 25% solution in methanol) were sequentially added and the reaction mixture was heated to reflux. After 6 h, the cooled reaction mixture was quenched with water, poured into water, and the organics were extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, were filtered, and were concentrated. The residue was purified by flash chromatography (20-60% ethyl acetate/hexanes) to provide the title compound (25%). ESIMS [M+H]<sup>+</sup>: 239.2.

b) 4-Biuret-[2,3']bithiophenyl-5-carboxylic acid methylamide

Ethyl allophanate (0.23 mmol) was added to a solution of 4-amino-[2,3']bithiophenyl-5-carboxylic acid methylamide (0.21 mmol) in dimethylsulfoxide (1.0 mL). After stirring at 80 °C for 65 h and 100 °C for 43 h, the reaction mixture was purified directly by Gilson reverse phase HPLC to afford the title product in low yield. ESIMS [M+H]<sup>+</sup>: 325.2.

### **Example 12**

#### **Preparation of 4-(3-Hydroxymethyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide**

a) 4-Ureido-[2,3']bithiophenyl-5-carboxylic acid methylamide

Following the procedure of Example 1 with 4-amino-[2,3']bithiophenyl-5-carboxylic acid methylamide afforded the title compound. ESIMS [M+H]<sup>+</sup>: 282.0.

b) 4-(3-Hydroxymethyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide

To a solution of 4-ureido-[2,3']bithiophenyl-5-carboxylic acid methylamide (0.060 mmol) in pyridine (0.5 mL) was added a 37% solution of formaldehyde (0.010 mL). The reaction mixture was heated at 50 °C for 18 h, then cooled, concentrated in vacuo, dissolved in DMSO, and purified by Gilson reverse phase HPLC to afford the title product in low yield. ESIMS [M+H]<sup>+</sup>: 312.2.

### **Example 13**

#### **Preparation of 5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide**

##### **a) 3-Amino-5-(4-methoxy-phenyl)-thiophene-2-carboxylic acid methylamide**

Using the procedure of Example 11(a) but replacing 1-thiophen-3-yl-ethanone with 4-methoxy-acetophenone provided the title compound.

##### **b) 5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide**

Following the procedure of Example 4 with 3-amino-5-(4-methoxy-phenyl)-thiophene-2-carboxylic acid methylamide provided the title compound. ESIMS [M+H]<sup>+</sup>: 291.0.

### **Example 14**

#### **Preparation of 5-(4-Methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid methylamide**

Following the procedure of Example 1 with 3-amino-5-(4-methoxy-phenyl)-thiophene-2-carboxylic acid methylamide provided the title compound. ESIMS [M+H]<sup>+</sup>: 306.0.

### **Example 15**

#### **Preparation of 5-(3,4-Dimethoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide**

a) 3-Amino-5-(3,4-dimethoxy-phenyl)-thiophene-2-carboxylic acid methylamide

Using the procedure of Example 11(a) but replacing 1-thiophen-3-yl-ethanone with 3,4-dimethoxy-acetophenone provided the title compound.

b) 5-(3,4-Dimethoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide

Following the procedure of Example 4 with 3-amino-5-(3,4-dimethoxy-phenyl)-thiophene-2-carboxylic acid methylamide provided the title compound. ESIMS  $[M+H]^+$ : 350.0.

#### **Example 16**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide

Following the procedure of Example 4 with 4-amino-[2,3']bithiophenyl-5-carboxylic acid methylamide provided the title compound. ESIMS  $[M+H]^+$ : 296.0.

#### **Example 17**

Preparation of 4-(3-Ethyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide

Following the procedure of Example 16 with ethyl isocyanate provided the title compound. ESIMS  $[M+H]^+$ : 310.2.

#### **Example 18**

Preparation of 5-(4-Amino-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide

a) 3-Amino-5-(4-nitro-phenyl)-thiophene-2-carboxylic acid methylamide

Using the procedure described in Example 11(a) but replacing 1-thiophen-3-yl-ethanone with 4-nitroacetophenone provided the title compound.

b) 5-(4-Nitro-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide

Following the procedure of Example 2 with 3-amino-5-(4-nitro-phenyl)-thiophene-2-carboxylic acid methylamide overnight provided the title compound. ESIMS  $[M+H]^+$ : 334.8.

c) 5-(4-Amino-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide

Palladium (22 mg of 10% Pd/C) was added to a solution of 5-(4-nitro-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide (0.066 mmol) in ethanol (5.0 mL). The reaction mixture was degassed and backfilled with argon three times and then degassed and backfilled with hydrogen gas (balloon) three times. The reaction mixture was then stirred at room temperature under a hydrogen balloon for 2h. The reaction mixture was filtered through Celite and rinsed three times with ethanol and three times with ethyl acetate. The combined filtrate was concentrated in vacuo, dissolved in DMSO, filtered, and purified by Gilson reverse phase HPLC to afford the title product. ESIMS  $[M+H]^+$ : 305.0.

#### **Example 19**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid phenylamide

Following the procedure described in Example 21(d) with aniline provided the title compound. ESIMS  $[M+H]^+$ : 358.0.

#### **Example 20**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzo[1,3]dioxol-5-ylamide

Following the procedure described in Example 21(d) with benzo[1,3]dioxol-5-ylamine provided the title compound. ESIMS  $[M+H]^+$ : 402.2.

**Example 21****Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (4-methoxy-phenyl)-amide****a) 4-Amino-[2,3']bithiophenyl-5-carboxylic acid methyl ester**

Using the procedure described in Example 11(a) but replacing *N*-methyl mercaptoacetamide with methyl mercaptoacetate provided the title compound.

**b) 4-Amino-[2,3']bithiophenyl-5-carboxylic acid**

4-Amino-[2,3']bithiophenyl-5-carboxylic acid methyl ester (17 mmol) was suspended in 1N aqueous lithium hydroxide solution (150 mL). The reaction mixture was heated at 70 °C for 24 h. The reaction mixture was then cooled to room temperature and extracted three times with ethyl acetate. The combined extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to yield 1.2 g of the title compound. The aqueous layer was neutralized with 12 M HCl (1 mL) and desired product precipitated out of solution. The white solid was filtered and dried to yield 1 g of the desired product. The remaining aqueous filtrate was extracted three times with ethyl acetate, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to yield another 1.1 g of the title compound. The combined products were concentrated in vacuo to yield a total of 3 g of desired product (88%) which was used directly in the next reaction without further purification. ESIMS [M+H]<sup>+</sup>: 227.0.

**c) 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid**

Following the procedure described in Example 2 with 4-amino-[2,3']bithiophenyl-5-carboxylic acid for overnight provided the title compound.

**d) 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (4-methoxy-phenyl)-amide**

4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (0.17 mmol) and benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate

(BOP, 0.17 mmol) were dissolved together in acetonitrile. This mixture was then treated with *p*-methoxyaniline (0.51 mmol) and triethylamine (0.85 mmol). The reaction mixture was stirred for 24 h at room temperature. The crude mixture was concentrated in vacuo, dissolved in DMSO, filtered, and purified by Gilson reverse phase HPLC to afford the title product. ESIMS  $[M+H]^+$ : 388.2.

#### **Example 22**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-hydroxy-phenyl)-amide

Following the procedure described in Example 21(d) with 2-amino-phenol provided the title compound. ESIMS  $[M+H]^+$ : 374.2.

#### **Example 23**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid ethylamide

Following the procedure described in Example 21(d) with ethylamine provided the title compound. ESIMS  $[M+H]^+$ : 310.0.

#### **Example 24**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid propylamide

Following the procedure described in Example 21(d) with *n*-propylamine provided the title compound. ESIMS  $[M+H]^+$ : 323.6.

#### **Example 25**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid isopropylamide

Following the procedure described in Example 21(d) with isopropylamine provided the title compound. ESIMS  $[M+H]^+$ : 324.4.

#### **Example 26**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid isobutyl-amide

Following the procedure described in Example 21(d) with isobutylamine provided the title compound. ESIMS  $[M+H]^+$ : 338.2.

#### **Example 27**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid pyrrolidin-3-ylamide

Following the procedure described in Example 21(d) with 3-aminopyrrolidine provided the title compound. ESIMS  $[M+H]^+$ : 350.8.

#### **Example 28**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-methoxyethyl)-amide

Following the procedure described in Example 21(d) with 2-methoxyethylamine provided the title compound. ESIMS  $[M+H]^+$ : 340.0.

#### **Example 29**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-aminoethyl)-amide

Following the procedure described in Example 21(d) with ethylenediamine provided the title compound. ESIMS  $[M+H]^+$ : 324.8.

**Example 30**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (3-dimethylamino-propyl)-amide

Following the procedure described in Example 21(d) with 3-dimethylaminopropylamine provided the title compound. ESIMS [M+H]<sup>+</sup>: 367.0.

**Example 31**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (3-amino-2-hydroxy-propyl)-amide

Following the procedure described in Example 21(d) with 1,3-diamino-2-propanol provided the title compound. ESIMS [M+H]<sup>+</sup>: 355.0.

**Example 32**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (pyridin-4-ylmethyl)-amide

Following the procedure described in Example 21(d) with 4-(aminomethyl)pyridine provided the title compound. ESIMS [M+H]<sup>+</sup>: 373.0.

**Example 33**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzylamide

Following the procedure described in Example 21(d) with benzylamine provided the title compound. ESIMS [M+H]<sup>+</sup>: 372.0.

**Example 34**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (furan-2-ylmethyl)-amide

Following the procedure described in Example 21(d) with furfurylamine provided the title compound. ESIMS  $[M+H]^+$ : 362.0.

### **Example 35**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (1H-imidazol-2-ylmethyl)-amide

Following the procedure described in Example 21(d) with (1H-imidazole-2-yl)-methylamine provided the title compound. ESIMS  $[M+H]^+$ : 362.0.

### **Example 36**

Preparation of 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

Following the procedure described in Example 21(d) with N-(2-aminoethyl)morpholine provided the title compound. ESIMS  $[M+H]^+$ : 395.0.

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below:

The present ligands can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is

preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art. The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound  $IC_{50}$ ,  $EC_{50}$ , the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be

administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula (I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease. As used herein, "diseases" treatable using the present compounds include, but are not limited to leukemias, solid tumor cancers and metastases, lymphomas, soft tissue cancers, brain cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, lung cancer, bladder cancer, bone cancer, prostate cancer, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, kidney cancer, head cancer and neck cancer, chronic inflammatory proliferative diseases such as psoriasis and rheumatoid arthritis; proliferative cardiovascular diseases such as restenosis; proliferative ocular disorders such as diabetic retinopathy; and benign hyperproliferative diseases such as hemangiomas.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for

example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the tests indicated hereinbelow.

**Chk1 Kinase Assay:**

Compounds capable of inhibiting Chk1 kinase can be identified with in vitro assays and cellular assays as described below. Variations of these assays would be obvious to those skilled in the art.

Streptavidin coated SPA beads, ATP and  $^{33}\text{P}$ -ATP were obtained from Amersham Pharmacia Biotech, Biotin labeled peptide KVSRSGLYRSPSPENLNRRK(Biotin-xx) $\text{NH}_2$  was obtained from Affiniti Research Products Ltd, assay buffer reagents were obtained from Sigma-Aldrich Co.Ltd. 96 well assay plates were obtained from Corning Inc. Assay buffer: 50 mM HEPES, 50 mM KCl, 5% Glycerol, 1 mM EGTA, 0.001% Tween-20; enzyme/peptide mix: 25 nM Chk1, 2.5  $\mu\text{M}$  biotin peptide, 7.5 mM 2-mercaptoethanol in assay buffer; ATP mix: 20  $\mu\text{M}$  ATP at 650kBq/mL, 5mM  $\text{MgCl}_2$  in assay buffer.

Inhibitors of decreasing concentration, from 10  $\mu\text{M}$  were incubated at room temperature for 1 hour together with 5  $\mu\text{L}$  enzyme/peptide mix and 5  $\mu\text{L}$  ATP mix. The reaction was stopped with 5  $\mu\text{L}$  of 0.5M EDTA followed by a further addition of 65  $\mu\text{L}$  of 0.2mg/mL SPA beads. Plates were spun at 2500 rpm for 10 minutes and the amount of  $^{33}\text{P}$  incorporated onto the peptide was quantified by a Wallac Trilux scintillation counter at a read time of 1 minute per well. IC50's were fitted to the data using SDM Explorer version 2.5 software (©GlaxoSmithKline Plc.).

#### **Expression of GST-Chk1:**

A GST-Chk1 expression construct was constructed which has the glutathione-S-transferase gene fused to the amino terminus of Chk1 kinase via a linker containing a thrombin cleavage site. This construct was cloned into the Baculovirus expression vector, pFASTBAC, and this was used to make the viral stock for the subsequent infection. *Spodoptera frugiperda* cells (Sf9) were infected with the virus expressing the GST-Chk1 and the cells were grown for 3 days, then harvested and frozen down.

#### **Purification of GST-Chk1:**

The GST-Chk1 protein was purified as follows: An Sf9 cell pellet expressing GST-Chk1 was resuspended on ice in lysis buffer (50mM Tris-Cl, pH 7.5, 250mM  $\text{NaCl}$ , 1mM dithiothreitol (DTT), 0.1%Brij, 5% (v/v) protease inhibitor cocktail, 1mM sodium orthovanadate), cells were lysed by sonication and centrifuged at

100,000xg for 30min. The supernatant was added to Glutathione Sepharose 4B, beads, equilibrated in wash buffer (20mM Tris-Cl, pH 7.0, 10mM MgCl<sub>2</sub>, 100mM NaCl<sub>2</sub>, 1mM DTT, 0.5%(v/v) protease inhibitor cocktail, 1mM sodium orthovanadate). The mixture was rocked for 30min. The resin with the bound GST-Chk1 was spun down at 500xg for 5min and washed with 14mls of wash buffer. The beads were spun as above and resuspended in another 14mls of wash buffer. The suspension was transferred into a column and allowed to pack, then the wash buffer was allowed to flow through by gravity. The GST-Chk1 was eluted from the column with 10mM Glutathione in 50mM Tris-Cl, pH 8.0 in 500ul fractions. Protein concentrations were determined on the fractions using Bio-Rad's Protein assay kit as per instructions. Fractions containing the GST-Chk1 were pooled and diluted to a concentration of ~0.5mg/ml and dialyzed for 4 hours at 4°C in dialysis buffer (20mM HEPES, pH 7.0, 1mM Manganese Acetate, 100mM NaCl<sub>2</sub>, 0.05% Brij-35, 10% glycerol, 1mM DTT, 0.2% (v/v) protease inhibitor cocktail, 1mM sodium orthovanadate). The protein was aliquoted and stored at -80°C.

### **Cell Cycle Studies:**

Drug studies considering cellular effects were performed in the HeLa S3 adherent cell line. Cells were plated at a concentration sufficiently low such that 24 hours later they were at 10-20% confluence (typically  $2 \times 10^5$  cells/15cm<sup>2</sup>). Cells were then synchronized in S phase by a repeated thymidine block. Briefly, cells were treated with 2mM thymidine for 18hours, released for 8 hours by 3 washes, and then treated again with thymidine. Following the second release from thymidine, 95% of cells were in S phase. Synchronized cells were then returned to complete media containing a DNA-damaging drug such as 50nM topotecan (a dosage we have found to be sufficient to arrest cells in early G2 phase without inducing apoptosis) alone and in combination with test compounds for up to 18 hours. Cell cycle profiles were then performed cytometrically using a procedure for propidium iodide staining of nuclei. (Vindelov et al, Cytometry Vol.3, No.5, 1983, 323-327) CHK1 inhibitors would be expected to reverse the G2 arrest caused by the DNA damaging agent. Typical concentration ranges for such activity would be 0.001 to 10  $\mu$ M.

**Proliferation/Apoptosis Studies:**

Proliferation studies were performed in a variety of adherent and non-adherent cell lines including Hela S3, HT29, and Jurkat. The proliferation assay utilized a colorimetric change resulting from reduction of the tetrazolium reagent XTT into a formazan product by metabolically active cells (Scudiero et al. Cancer Research, 48, 1981, 4827-4833) Cells were seeded in 100ul in 96 well plates to roughly 10% confluence (cell concentration varied with cell lines) and grown for 24 hours. Compounds were then added with or without sufficient vehicle- containing media to raise the cells to a 200ul final volume containing chemical reagents in 0.2% DMSO. Cells received multiple concentrations of DNA-damaging anti-proliferative drugs such as topotecan, test compounds, and combination treatment at 37°C 5% CO<sub>2</sub>. 72 hours later, 50 uls of an XTT/ phenazine methosulfate mixture were added to each well and cells were left to incubate for 90mins. Plate was read at 450nm, and anti-proliferative effects were compared relative to vehicle treated cells. CHK1 inhibitors are expected to enhance the cytotoxicity of DNA-damaging chemotherapeutic drugs. Typical concentration ranges for such activity would be 0.001 to 10 uM. Other assays for cellular proliferation or cytotoxicity could also be used with test compounds, and these assays are known to those skilled in the art.

**Ikk- $\beta$  Kinase Assay**

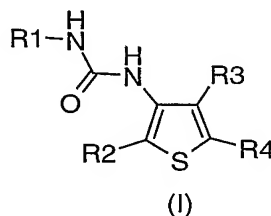
IKK- $\beta$  was expressed as a GST-tagged protein, and its activity was assessed in a 96-well scintillation proximity assay (SPA). Briefly, IKK- $\beta$  was diluted in assay buffer (20 mM Hepes, pH 7.7, 2 mM MgCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 10 mM  $\beta$ -glycerophosphate, 10 mM NaF, 10 mM PNPP, 0.3 mM Na<sub>3</sub>VO<sub>4</sub>, 1 mM benzamidine, 2  $\mu$ M PMSF, 10  $\mu$ g/ml aprotinin, 1 ug/mL leupeptin, 1 ug/mL pepstatin, 1mM DTT; 20 nM final), with various concentrations of compound or DMSO vehicle, 240 nM ATP and 200 nCi [<sup>33</sup>P]-ATP (10 mCi/mL, 2000 Ci/mmol; NEN Life Science Products, Boston, MA). The reaction was started with the addition of a biotinylated peptide comprising amino acids 15 – 46 of I $\kappa$ B- $\alpha$  (American Peptide) to a final concentration of 2.4  $\mu$ M, in a total volume of 50 uL.

The sample incubated for one hour at 30 °C, followed by the addition of 150 uL of stop buffer (PBS w/o  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , 0.1% Triton X-100 (v/v), 10 mM EDTA) containing 0.2 mg streptavidin-coated SPA PVT beads (Amersham Pharmacia Biotech, Piscataway, NJ). The sample was mixed, incubated for 10 min. at room temperature, centrifuged (1000 xg, 2 minutes), and measured on a Hewlett-Packard TopCount.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A method of inhibiting angiogenesis or damage response kinase activity which comprises administering to a subject in need thereof, an effective amount of a compound according to Formula (I) hereinbelow:



wherein:

R1 is selected from the group consisting of H, C<sub>1-2</sub> alkyl, XH, XCH<sub>3</sub>, C<sub>1-2</sub> alkyl-XH, C<sub>1-2</sub> alkyl-XCH<sub>3</sub>, C(O)NH<sub>2</sub>, C(O)NHCH<sub>3</sub>, and C(O)-C<sub>1-2</sub> alkyl;

X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of C(O)R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, C(O)NHR<sup>5</sup>, C(O)NHC(=NH)R<sup>5</sup>, C(O)NHC(=NH)NR<sup>5</sup>R<sup>6</sup>, C(O)NHC(O)R<sup>5</sup>, C(O)NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>5</sup>, S(O)R<sup>5</sup>, SO<sub>3</sub>R<sup>5</sup>, and PO<sub>3</sub>R<sup>5</sup>R<sup>6</sup>;

R<sup>5</sup> and R<sup>6</sup> are, independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, and C<sub>0-6</sub> alkylheteroaryl, or R<sup>5</sup> and R<sup>6</sup>, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl, wherein any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position;

A is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, C<sub>0-6</sub> alkylheteroaryl, C(=NH)R<sup>7</sup>, COR<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>,

$C(S)R^7$ , cyano, trifluoromethyl,  $NR^7R^8$ ,  $N(O)R^7R^8$ ,  $NR^7R^8R^9Y$ ,  $NR^7COR^7$ ,  $NR^7CONR^7R^8$ ,  $NR^7CON(O)R^7R^8$ ,  $NR^7CONR^7R^8R^9Y$ ,  $NR^7CO_2R^7$ ,  $NR^7C(O)SR^7$ ,  $NR^7SO_2R^7$ ,  $NR^7SO_2NR^7R^8$ , nitro,  $OR^7$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^7$ ,  $S(O)R^7$ ,  $S(O)_2R^7$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^7R^8$ ,  $SO_3R^7$ ,  $PO_3R^7R^8$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $(CH_2)_{0-6}$  heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion;

D is selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $C(=NH)R^7$ ,  $COR^7$ ,  $CONR^7R^8$ ,  $CON(O)R^7R^8$ ,  $CONR^7R^8R^9Y$ ,  $CO_2R^7$ ,  $C(O)SR^7$ ,  $C(S)R^7$ , cyano, trifluoromethyl,  $NR^7R^8$ ,  $N(O)R^7R^8$ ,  $NR^7R^8R^9Y$ ,  $NR^7COR^7$ ,  $NR^7CONR^7R^8$ ,  $NR^7CON(O)R^7R^8$ ,  $NR^7CONR^7R^8R^9Y$ ,  $NR^7CO_2R^7$ ,  $NR^7C(O)SR^7$ ,  $NR^7SO_2R^7$ ,  $NR^7SO_2NR^7R^8$ , nitro,  $OR^7$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^7$ ,  $S(O)R^7$ ,  $S(O)_2R^7$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^7R^8$ ,  $SO_3R^7$ ,  $PO_3R^7R^8$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $(CH_2)_{0-6}$  heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

$R^7$ ,  $R^8$ , and  $R^9$  are, independently, selected from the group consisting of hydrogen,  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl, and  $C_{0-6}$  alkylheteroaryl, or  $R^7$  and  $R^8$ , taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen,  $C_{1-6}$  alkyl or  $(CH_2)_{0-3}$  aryl, wherein any of the foregoing may be optionally substituted by one or more of group E and on any position;

E is selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $C(=NH)R^{10}$ ,  $COR^{10}$ ,  $CONR^{10}R^{11}$ ,  $CON(O)R^{10}R^{11}$ ,  $CONR^{10}R^{11}R^{12}Y$ ,  $CO_2R^{10}$ ,  $C(O)SR^{10}$ ,

$C(S)R^{10}$ , cyano, trifluoromethyl,  $NR^{10}R^{11}$ ,  $N(O)R^{10}R^{11}$ ,  $NR^{10}R^{11}R^{12}Y$ ,  $NR^{10}COR^{10}$ ,  
 $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}CON(O)R^{10}R^{11}$ ,  $NR^{10}CONR^{10}R^{11}R^{12}Y$ ,  $NR^{10}CO_2R^{10}$ ,  
 $NR^{10}C(O)SR^{10}$ ,  $NR^{10}SO_2R^{10}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ , nitro,  $OR^{10}$ ,  $OCF_3$ , aryloxy,  
heteroaryloxy,  $SR^{10}$ ,  $S(O)R^{10}$ ,  $S(O)_2R^{10}$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^{10}R^{11}$ ,  
 $SO_3R^{10}$ ,  $PO_3R^{10}R^{11}$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$   
alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl  
may be optionally substituted by one or more of  $C(=NH)R^{10}$ ,  $COR^{10}$ ,  $CONR^{10}R^{11}$ ,  
 $CON(O)R^{10}R^{11}$ ,  $CONR^{10}R^{11}R^{12}Y$ ,  $CO_2R^{10}$ ,  $C(O)SR^{10}$ ,  $C(S)R^{10}$ , cyano, trifluoromethyl,  
 $NR^{10}R^{11}$ ,  $N(O)R^{10}R^{11}$ ,  $NR^{10}R^{11}R^{12}Y$ ,  $NR^{10}COR^{10}$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}CON(O)R^{10}R^{11}$ ,  
 $NR^{10}CONR^{10}R^{11}R^{12}Y$ ,  $NR^{10}CO_2R^{10}$ ,  $NR^{10}C(O)SR^{10}$ ,  $NR^{10}SO_2R^{10}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ ,  
nitro,  $OR^{10}$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^{10}$ ,  $S(O)R^{10}$ ,  $S(O)_2R^{10}$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  
 $S(O)_2CF_3$ ,  $SO_2NR^{10}R^{11}$ ,  $SO_3R^{10}$ ,  $PO_3R^{10}R^{11}$ , or halo, and on any position;  
 $R^{10}$ ,  $R^{11}$ , and  $R^{12}$  are, independently, selected from the group consisting of hydrogen,  
 $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  
 $C_{0-6}$  alkylheterocyclyl, and  $C_{0-6}$  alkylheteroaryl, or  $R^{10}$  and  $R^{11}$ , taken together with the  
nitrogen to which they are attached, forms a ring having 3 to 7 carbon atoms  
optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen,  
or nitrogen, substituted with hydrogen,  $C_{1-6}$  alkyl or  $(CH_2)_{0-3}$ aryl; or a  
pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug of  
formula (I).

2. A method according to claim 1 wherein  $R_3$  is H.
3. A method according to claim 2 wherein  $R_1$  is H or  $CH_3$ .
4. A method according to claim 2 wherein Y is selected from the group consisting of bisulfate, chloride, fumarate, iodide, maleate, methanesulfonate, nitrate, trifluoromethanesulfonate, and sulfate.
5. A method according to claim 4 wherein the compound is selected from the group consisting of:

4-Ureido-[2,3']bithiophenyl-5-carboxylic acid amide  
5-(4-Methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid amide  
5-(4-Fluoro-phenyl)-3-ureido-thiophene-2-carboxylic acid amide  
5-Phenyl-3-ureido-thiophene-2-carboxylic acid methyl ester  
1-(2-Acetyl-5-phenyl-thiophen-3-yl)-3-methyl-urea  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid amide  
5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid amide  
3-(3-Methyl-ureido)-5-phenyl-thiophene-2-carboxylic acid methyl ester  
5-(4-Fluoro-phenyl)-3-ureido-thiophene-2-carboxylic acid methyl ester  
(2-Acetyl-5-phenyl-thiophen-3-yl)-urea  
5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
5-(4-Methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid methylamide  
5-(3,4-Dimethoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide  
4-(3-Ethyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide  
4-biuret-[2,3']bithiophenyl-5-carboxylic acid methylamide  
  
5-(4-Amino-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide  
4-(3-Hydroxymethyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid phenylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzo[1,3]dioxol-5-ylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (4-methoxy-phenyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-hydroxy-phenyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid ethylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid propylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid isopropylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid isobutyl-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid pyrrolidin-3-ylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-methoxy-ethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-amino-ethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (3-dimethylamino-propyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (3-amino-2-hydroxy-propyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (pyridin-4-ylmethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzylamide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (furan-2-ylmethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (1*H*-imidazol-2-ylmethyl)-amide  
4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

6. A method according to claim 4 wherein the compound is selected from the group consisting of:

- 4-Ureido-[2,3']bithiophenyl-5-carboxylic acid amide
- 5-(4-Methoxy-phenyl)-3-ureido-thiophene-2-carboxylic acid amide
- 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid amide
- 5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid amide
- 5-(4-Methoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide
- 5-(3,4-Dimethoxy-phenyl)-3-(3-methyl-ureido)-thiophene-2-carboxylic acid methylamide
- 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid methylamide
- 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid phenylamide
- 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid benzo[1,3]dioxol-5-ylamide
- 4-(3-Methyl-ureido)-[2,3']bithiophenyl-5-carboxylic acid (2-amino-ethyl)-amide

7. A method according to claim 1 wherein the kinase being inhibited is chk-1 kinase.

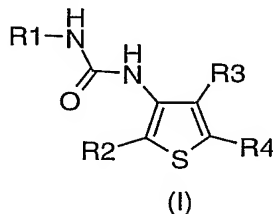
8. A method according to claim 1 wherein the present compounds are administered as IKK $\beta$ /Chk1 kinase dual inhibitors for the treatment of cancer and cancer-related diseases.

9. A method according to claim 1 wherein the disease or disorder being treated is selected from the group consisting of leukemia, solid tumor cancer, metastases, lymphomas, soft tissue cancers, brain cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, lung cancer, bladder cancer, bone cancer, prostate cancer, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, kidney cancer, head cancer and neck cancer, chronic inflammatory proliferative diseases, proliferative cardiovascular diseases, proliferative ocular disorders and benign hyperproliferative diseases.

10. A method according to claim 9 wherein the disease or disorder treated is selected from the group consisting of psoriasis, rheumatoid arthritis, diabetic retinopathy and hemangiomas.

10. A method according to claim 9 wherein the disease or disorder treated is selected from the group consisting of psoriasis, rheumatoid arthritis, diabetic retinopathy and hemangiomas.

11. A compound according to Formula (I) hereinbelow:



wherein:

R1 is selected from the group consisting of H, C<sub>1-2</sub> alkyl, XH, XCH<sub>3</sub>, C<sub>1-2</sub> alkyl-XH, C<sub>1-2</sub> alkyl-XCH<sub>3</sub>, C(O)NH<sub>2</sub>, C(O)NHCH<sub>3</sub>, and C(O)-C<sub>1-2</sub> alkyl, provided that when R1 is H, R2 is not CONH<sub>2</sub>, or provided that when R1 is C<sub>1-2</sub> alkyl, R2 is not CONH<sub>2</sub>; with the preferred substitution being H or CH<sub>3</sub>;

X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of C(O)R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, C(O)NHR<sup>5</sup>, C(O)NHC(=NH)R<sup>5</sup>, C(O)NHC(=NH)NR<sup>5</sup>R<sup>6</sup>, C(O)NHC(O)R<sup>5</sup>, C(O)NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>5</sup>, S(O)R<sup>5</sup>, SO<sub>3</sub>R<sup>5</sup>, and PO<sub>3</sub>R<sup>5</sup>R<sup>6</sup>;

R<sup>5</sup> and R<sup>6</sup> are, independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>0-6</sub> alkylaryl, C<sub>0-6</sub> alkylheterocyclyl, and C<sub>0-6</sub> alkylheteroaryl, or R<sup>5</sup> and R<sup>6</sup>, taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl, wherein any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen; with the preferred substitution being H;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position, provided that when R1 is CH<sub>3</sub> and R2 is CO<sub>2</sub>R<sup>5</sup>, R4 is not phenyl, or provided that when R1 is H, R4 is not 4-pyridyl;

A is selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $C(=NH)R^7$ ,  $COR^7$ ,  $CONR^7R^8$ ,  $CON(O)R^7R^8$ ,  $CONR^7R^8R^9Y$ ,  $CO_2R^7$ ,  $C(O)SR^7$ ,  $C(S)R^7$ , cyano, trifluoromethyl,  $NR^7R^8$ ,  $N(O)R^7R^8$ ,  $NR^7R^8R^9Y$ ,  $NR^7COR^7$ ,  $NR^7CONR^7R^8$ ,  $NR^7CON(O)R^7R^8$ ,  $NR^7CONR^7R^8R^9Y$ ,  $NR^7CO_2R^7$ ,  $NR^7C(O)SR^7$ ,  $NR^7SO_2R^7$ ,  $NR^7SO_2NR^7R^8$ , nitro,  $OR^7$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^7$ ,  $S(O)R^7$ ,  $S(O)_2R^7$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^7R^8$ ,  $SO_3R^7$ ,  $PO_3R^7R^8$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $(CH_2)_{0-6}$ heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion;

D is selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $C(=NH)R^7$ ,  $COR^7$ ,  $CONR^7R^8$ ,  $CON(O)R^7R^8$ ,  $CONR^7R^8R^9Y$ ,  $CO_2R^7$ ,  $C(O)SR^7$ ,  $C(S)R^7$ , cyano, trifluoromethyl,  $NR^7R^8$ ,  $N(O)R^7R^8$ ,  $NR^7R^8R^9Y$ ,  $NR^7COR^7$ ,  $NR^7CONR^7R^8$ ,  $NR^7CON(O)R^7R^8$ ,  $NR^7CONR^7R^8R^9Y$ ,  $NR^7CO_2R^7$ ,  $NR^7C(O)SR^7$ ,  $NR^7SO_2R^7$ ,  $NR^7SO_2NR^7R^8$ , nitro,  $OR^7$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^7$ ,  $S(O)R^7$ ,  $S(O)_2R^7$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^7R^8$ ,  $SO_3R^7$ ,  $PO_3R^7R^8$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $(CH_2)_{0-6}$ heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

$R^7$ ,  $R^8$ , and  $R^9$  are, independently, selected from the group consisting of hydrogen,  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl, and  $C_{0-6}$  alkylheteroaryl, or  $R^7$  and  $R^8$ , taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen,  $C_{1-6}$  alkyl or  $(CH_2)_{0-3}$ aryl, wherein any of the foregoing may be optionally substituted by one or more of group E and on any position;

E is selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl,  $C(=NH)R^{10}$ ,  $COR^{10}$ ,  $CONR^{10}R^{11}$ ,  $CON(O)R^{10}R^{11}$ ,  $CONR^{10}R^{11}R^{12}Y$ ,  $CO_2R^{10}$ ,  $C(O)SR^{10}$ ,  $C(S)R^{10}$ , cyano, trifluoromethyl,  $NR^{10}R^{11}$ ,  $N(O)R^{10}R^{11}$ ,  $NR^{10}R^{11}R^{12}Y$ ,  $NR^{10}COR^{10}$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}CON(O)R^{10}R^{11}$ ,  $NR^{10}CONR^{10}R^{11}R^{12}Y$ ,  $NR^{10}CO_2R^{10}$ ,  $NR^{10}C(O)SR^{10}$ ,  $NR^{10}SO_2R^{10}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ , nitro,  $OR^{10}$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^{10}$ ,  $S(O)R^{10}$ ,  $S(O)_2R^{10}$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^{10}R^{11}$ ,  $SO_3R^{10}$ ,  $PO_3R^{10}R^{11}$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl,  $C_{0-6}$  alkylheteroaryl may be optionally substituted by one or more of  $C(=NH)R^{10}$ ,  $COR^{10}$ ,  $CONR^{10}R^{11}$ ,  $CON(O)R^{10}R^{11}$ ,  $CONR^{10}R^{11}R^{12}Y$ ,  $CO_2R^{10}$ ,  $C(O)SR^{10}$ ,  $C(S)R^{10}$ , cyano, trifluoromethyl,  $NR^{10}R^{11}$ ,  $N(O)R^{10}R^{11}$ ,  $NR^{10}R^{11}R^{12}Y$ ,  $NR^{10}COR^{10}$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}CON(O)R^{10}R^{11}$ ,  $NR^{10}CONR^{10}R^{11}R^{12}Y$ ,  $NR^{10}CO_2R^{10}$ ,  $NR^{10}C(O)SR^{10}$ ,  $NR^{10}SO_2R^{10}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ , nitro,  $OR^{10}$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^{10}$ ,  $S(O)R^{10}$ ,  $S(O)_2R^{10}$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^{10}R^{11}$ ,  $SO_3R^{10}$ ,  $PO_3R^{10}R^{11}$ , or halo, and on any position;  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$  are, independently, selected from the group consisting of hydrogen,  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{0-6}$  alkylaryl,  $C_{0-6}$  alkylheterocyclyl, and  $C_{0-6}$  alkylheteroaryl; or  $R^{10}$  and  $R^{11}$ , taken together with the nitrogen to which they are attached, forms a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen,  $C_{1-6}$  alkyl or  $(CH_2)_{0-3}$ aryl; or a pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug of formula (I).

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/31901

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/506

US CL : 514/252.01, 252.05, 255.05, 256; 548/190, 233, 326.5, 557

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/252.01, 252.05, 255.05, 256; 548/190, 233, 326.5, 557

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN; reg, structure search

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,823,161 A (LESSER) 09 July 1974 (09.07.1974), see entire document.	11
Y	WO 01/58890 A1 (ASTRAZENECA AB) 16 August 2001 (16.08.2001), see entire document, especially page 18, lines 7-18.	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

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"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

11 December 2002 (11.12.2002)

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Name and mailing address of the ISA/US

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